Previous Rejections Maintained from June 22, 2001 Office Action

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 18-39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Action maintains the specification is enabling for single-chain antibody-streptavidin fusion proteins. In particular, the Action states the specification is enabled for the single-chain antibody-streptavidin fusion proteins huNR-LU-10 scFvSA and B9E9 scFvSA. The Action maintains the state of the art of protein engineering is unpredictable and the specification lacks sufficient guidance for one skilled in the art to make all of the claimed fusion proteins with a reasonable expectation of success and without undue experimentation.

Applicants traverse this ground for rejection. Applicants submit the specification adequately describes the invention such that one skilled in the art could practice the claimed invention. In particular, Applicants point out the description how to generate genomic streptavidin fusion proteins at line 16, page 8—line 10, page 17 and in Examples I-X of the specification. Furthermore, Applicants submit the specification discloses methods of testing the ability of a fusion protein to bind biotin and maintain solubility in the periplasmic space are well known in the art. More specifically, the specification states measuring biotin binding capacity and biotin dissociation rate are well known in the art and can be tested by a variety of means, including labeling the fusion protein with a subsaturating level of radiolabeled biotin, then adding a 100-fold saturating level of biocytin to initiate dissociation. The free radiolabeled biotin is measured at timed intervals. *See* lines 16-19, page 9 and lines 1-12, page 11 of the instant specification.

Nevertheless, without acquiescing to the grounds for rejection but solely to expedite prosecution of the application, Applicants have amended Claims 18 and 24-26 to focus on one aspect of the inventive subject matter. Thus, Applicants respectfully request this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claim 65 stands rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants thank the Examiner for pointing out this matter.

Applicants submit due to an oversight, claim 65 was not amended as Applicants stated in the reply to the Office Action of June 22, 2001. While, Applicants maintain that pharmaceutical compositions are enabled, and other compositions are contemplated. Nevertheless, Applicants have amended Claim 65 to recite "composition", rather than "pharmaceutical composition". Applicants respectfully request this rejection be withdrawn, and apologize for the oversight.

Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 18-22, 38, 39 and 65 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Action alleges the written description of the invention describes antibody-streptavidin fusion proteins, but doesn't describe enough species to claim any and all fusion proteins.

Applicants traverse this ground for rejection. In particular, Applicants note the Action of June 22, 2001 cites *Regents of the University of California v Eli Lilly* (43 USPQ2d 1398-1412) wherein the court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus 'requires a precise definition, such as by structure, formula, chemical name, or physical properties'.

Applicants submit the multiple species of the claimed invention adequately describe the genus of genomic streptavidin fusion proteins of the claimed invention. As indicated in independent Claim 18, the physical properties of the fusion protein are such that a first polypeptide comprises at least 129 amino acids of streptavidin, as set forth in SEQ ID NO:2, or functional variants, said variants comprising at least 90% amino acid identity with the native sequence thereof, wherein said variants retain the ability to bind biotin, and wherein said second polypeptide is an antibody or antigen-binding fragment thereof. Applicants further submit the genomic streptavidin fusion protein is capable of being expressed in the periplasmic space of a bacterial host, which is contrary to core streptavidin fusion proteins that are expressed in inclusion bodies in bacterial hosts. *See* line 4, page 11 of the instant specification. In addition, there is no reasonable expectation that the streptavidin molecule could not be fused to virtually any other protein. Applicants submit these multiple physical properties adequately describe the

genus that encompasses the particular species listed in the specification, in particular in Examples I-X.

Rejection under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claim 24 stands rejected under 35 U.S.C. § 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Action states Claim 24 is unclear as to whether the phrase "capable of forming a tetrameric complex" means the fusion protein must form a tetrameric complex or rather that the fusion protein has the potential to form a tetrameric complex. In addition, the Action states Claim 24 is indefinite because the phrase "a first and a second polypeptide joined end to end" is unclear with regard to whether the first and second polypeptides are the amino-terminal polypeptide and carboxyl-terminal polypeptide, respectively, or are merely different polypeptides.

Applicants respectfully traverse these rejections. Applicants submit support for a fusion protein capable of forming a tetrameric complex is provided on page 9, lines 20-24. Applicants submit the fusion protein has the potential to form a tetrameric complex and the phrase "capable of forming" is co-extensive with the phrase "has the potential to form". Without acquiescing to the grounds for rejection, Applicants have amended Claim 24 to recite "forms a tetrameric complex." Further, as to the formation of the complex, Applicants submit that one of skill in the art would understand the complex to be non-covalent, as is the case with the native streptavidin complex formation.

Furthermore, with regard to the phrase "a first and a second polypeptide joined end to end" Applicants submit, as previously and successfully argued for Claim 18 in the response to the June 22, 2001 Office Action, one skilled in the art would understand the phrase is meant merely to distinguish one polypeptide from the other, without limiting the first polypeptide to the N-terminus of the fusion protein, or the second polypeptide to the C-terminus. Applicants would like to thank the Examiner for withdrawing this same grounds for rejection of Claim 18 of the June 22, 2001 Office Action, and would respectfully request this rejection be reconsidered and withdrawn for Claim 24.

Rejection under 35 U.S.C. § 103(a), Obviousness

Claims 18-39 and 65 stand rejected under 35 U.S.C. §103 (a) as being allegedly unpatentable over Dubel, *et al.* (J. Imm. Meth. 178: 201-209, 1995), as evidenced by Kipriyanov, *et al.* (Hum. Antibod. Hybrid. 6: 93-101, 1995), in view of Desplancq, *et al.* (Prot. Eng. 7: 1027-1033, 1994), Anderson, *et al.* (Clin. Immnol. Immunopath. 84: 73-84, 1997), McLaughlin, *et al.* (Onc. 12: 1763-1769, 1998), the internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia), Gallizia *et al.* (Prot. Exp. Pur. 14: 192-196, 1998), and Pahler, *et al.* (J. Biol. Chem. 262: 13933-13937, 1987), Aragarana, *et al.* (Nuc. Acids Res. 14: 1871-1882, 1986), Ohno *et al.* (DNA and Cell Biol. 15: 401-406, 1996), and Goshorn, *et al.* (Canc. Res. 53: 2123-2127, 1993).

Applicants respectfully submit the cited references, either alone or in combination, do not teach or suggest all elements of the claimed invention. The Action claims, in particular, that Applicants have failed to address the obviousness of the *combination* of references but instead, in the previous response to the June 22, 2001 Office Action, only addressed the cited prior art references individually.

Applicants traverse this ground for rejection. Applicants respectfully point out the Federal Circuit has held a *prima facie* case of obviousness based on the prior art can only be established by showing an objective teaching in the prior art or general knowledge of one skilled in the art that *would lead* that individual to combine the relevant teachings of the cited references (emphasis original). That is, the teachings of references can be combined only if there is some suggestion or incentive to do so. Furthermore, the court held "obvious to try" is not a legitimate test of patentability. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Applicants submit nothing in the eleven cited prior art references would lead one of ordinary skill in the art to combine all eleven cited references to arrive at the claimed invention.

Applicants submit neither Dubel *et al.*, nor Kipiryanov *et al.*, nor Desplancq *et al.*, nor Anderson *et al.*, nor McLaughlin *et al.*, nor Bioprobe BV Catalog of Mouse Hybridomas, nor Gallizia *et al.*, nor Pahler *et al.*, nor Aragarana *et al.*, nor Ohno *et al.*, nor Goshorn *et al.* alone or in combination disclose genomic streptavidin fusion proteins as disclosed in the presently claimed invention. Furthermore, nothing in the cited references would lead one of ordinary skill

in the art to combine the references to arrive at the genomic streptavidin fusion proteins of the presently claimed invention.

The Action alleges Dubel *et al.* teaches a first fusion protein capable of forming a tetrameric complex with a second, third, and fourth fusion protein wherein the fusion proteins comprise a first polypeptide comprising a portion of streptavidin and a second polypeptide comprising a fragment of an antibody that specifically binds a cell-associated stromal or matrix protein. Applicants submit Dubel *et al.* discloses core streptavidin fusion proteins, not genomic streptavidin fusion proteins as is disclosed in the claimed invention.

Furthermore, the Action states Kipriyanov *et al.* teaches single-chain antibodies joined with core streptavidin, and such antibody-core streptavidin fusion proteins are capable of forming a tetramer which binds biotin with greater avidity than monomers. Applicants submit Kipriyanov *et al.* teaches away from the claimed invention by disclosing exactly what the Action quotes, "deletions of several amino acids from the N-/C-terminus resulting in core-streptavidin molecule did not influence the biotin binding." Indeed, this core-streptavidin of amino acids 14-136 is what is used in the cited prior art references and is not what the claimed invention encompasses.

The Action alleges the claimed invention is rendered obvious in part under Dubel *et al.* in light of Arragarana *et al.* which teaches the first 24 amino-terminal amino acids compose a signal sequence that is cleaved and because Pahler *et al.* teaches approximately the next 13 amino acids of streptavidin are susceptible to protease cleavage.

Applicants submit these cited prior art references do not render the presently claimed invention obvious. Applicants reiterate the presently claimed invention discloses genomic streptavidin fusion proteins, whereas Dubel *et al*, Arragarana *et al.*, and Pahler *et al.*, disclose core streptavidin fusion proteins. Furthermore, Applicants submit the Action misinterprets Arragarana *et al.* and Pahler *et al.* since the present state of the art uses core-streptavidin fusion proteins precisely because prior art such as Arragarana *et al.* and Pahler *et al.* disclose the N-terminal and C-terminal amino acids can be discarded without streptavidin loss of ability to bind biotin. Applicants submit such prior art clearly teaches away from the claimed invention of genomic streptavidin fusion proteins which include N-terminal and/or C-terminal amino acids and teaches no advantages of including the signal sequence.

Applicants submit genomic streptavidin fusion proteins provide substantial and heretofore unrecognized advantages over core streptavidin fusion proteins, including protein folding and secretion into the periplasmic space. Such advantages circumvent the need to extract the protein from the cytoplasm, as is necessary for core-streptavidin fusion proteins. Applicants submit the use of genomic streptavidin in fusion proteins remedies a short-coming of using core-streptavidin in fusion proteins and was surprising in light of the prior art, which consistently used core-streptavidin.

The Action states that such unexpected findings are instead another advantage which would flow naturally from following the suggestion of the prior art. Applicants submit the Action fails to distinguish between core-streptavidin fusion proteins of the prior art and genomic streptavidin fusion proteins of the claimed invention.

Applicants point out the definitions from lines 14-22, page 6 of the instant specification:

""Core streptavidin," as used herein, refers to a streptavidin molecule consisting of the central amino acid residues 14-136 of streptavidin of Figure 4 and also of Figure 3 of U.S. Patent No. 4,839,293 and deposited at ATCC number X03591.

"Genomic streptavidin," as used herein, refers to a sequence comprising at least 124 residues of the sequence set forth in Figure 4. Accordingly, genomic streptavidin refers to streptavidin molecules that have N-terminal, C-terminal, or both N- and C-terminal extensions of core streptavidin. The N- and C-terminal extensions may comprise any number of amino acids selected from 1 to 13, 137 to 159, and in some cases -1 to -24 of Figure 4."

Applicants submit the present state of the art is such that preparations of streptavidin expressed gene fusions are usually made by expressing a core streptavidin-containing construct in bacteria, wherein inclusion bodies are formed. Such production has several disadvantages, including the rigor and expense of purifying from inclusion bodies, the necessity of using harsh denaturing agents such as guanidine hydrochloride, and the difficulty in scaling up in an economical fashion.

Therefore, there exists a need in the art for easy, cost effective, and scaleable methods for the production of streptavidin fusion proteins. Accordingly, the present invention provides several key advantages. For example, in one embodiment, a genomic streptavidin expressed gene fusion is expressed as a soluble protein into the periplasmic space of bacteria and

undergoes spontaneous folding. Accordingly, such expression offers the advantage that the periplasm is a low biotin environment and one need not purify and refold the protein under harsh denaturing conditions that may prove fatal to the polypeptide encoded by a heterologous nucleic acid molecule fused to the genomic streptavidin nucleic acid molecule. The present invention fulfills this need, while further providing other related advantages. *See* lines 19-26, page 2 of the instant specification.

Applicants submit the prior art references *individually or combined* do not disclose the genomic streptavidin fusion proteins of the presently claimed invention. Applicants submit instead the *combined* prior art references teach away from the claimed invention by disposing of the N-terminal and C-terminal amino acids of streptavidin, forming core-streptavidin, whereas the claimed invention incorporates the N-terminal and/or C-terminal amino acids to form genomic streptavidin. Thus, Applicants submit the presently claimed invention is non-obvious in light of the cited prior art references. Applicants respectfully request this rejection be reconsidered and withdrawn.

New Grounds of Claim Rejections

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 18-39 and 65 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. The Action concedes the specification is enabling for antibody-streptavidin fusion proteins, namely huNR-LU-10 scFvSA and B9E9 scFvSA.

Applicants traverse this ground for rejection and reiterate the remarks presented above. Applicants submit the specification adequately describes the invention such that one skilled in the art could practice the invention. In particular, Applicants point out the description of how to generate genomic streptavidin fusion proteins at line 16, page 8—line 10, page 17 and in Examples I-X of the specification. Furthermore, Applicants submit the specification discloses methods of testing the ability of a fusion protein to bind biotin and maintain solubility in the periplasmic space are well known in the art. Accordingly, Applicants respectfully request the rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claim 24 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which is the

invention. In particular, the Action stated Claim 24 is unclear because the claim recites the phrase "a tetrameric complex similar to that of native streptavidin".

Applicants traverse this ground for rejection. Applicants submit the phrase "a tetrameric complex similar to that of native streptavidin" would be fully understood by one skilled in the art. Support for this can be found at lines 1-21, page 1 of the specification. Nevertheless, without acquiescing to the grounds for rejection but rather solely to expedite prosecution of the application, Applicants have amended Claim 24 to remove the phrase "similar to that of native streptavidin".

Applicants respectfully submit that all claims pending in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 23 has been canceled.

Claims 18, 24-26 and 65 have been amended as follows:

18. (Twice amended) A genomic streptavidin fusion protein, comprising at least a first and a second polypeptide joined end to end, wherein said first polypeptide comprises at least 129 amino acids of streptavidin, as set forth in SEQ ID NO:2, or functional variants, said variants comprising at least 90% amino acid identity with the native sequence thereof, wherein said variants retain the ability to bind biotin, and wherein said second polypeptide is an antibody or antigen-binding fragment of an antibody [comprises an amino acid sequence differing by at least one residue from said first polypeptide].

24. (Twice amended) The genomic streptavidin fusion protein of claim 18, wherein said fusion protein [is capable of forming] forms a tetrameric complex [similar to that of native streptavidin] with a second, third, and fourth fusion protein, said second, third, and fourth fusion protein comprising at least a first and second polypeptide joined end to end, wherein said first polypeptide comprises at least 129 amino acids of streptavidin, as set forth in SEQ ID NO:2, or functional variants, said variants comprising at least 90% amino acid identity with the native sequence thereof, wherein said variant retains the ability to bind biotin, and wherein said second polypeptide is an antibody or antigen-binding fragment thereof [comprises an amino acid sequence differing by at least one residue from said first polypeptide].

25. (Amended) The fusion protein of claim [23] 18, wherein the antibody is B9E9.

26. (Twice Amended) The fusion protein of claim [23] 18 wherein the antibody is a single-chain Fv fragment.

65. (Amended) A [pharmaceutical] composition, comprising the fusion protein of any one of claims 18-22 and 24-39.

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